

The 2015 CUA-CUOG Guidelines for the management of castration-resistant prostate cancer (CRPC)

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Summary

Agents that have shown improvements in survival in mCRPC now include abiraterone, enzalutamide, docetaxel, cabazitaxel and radium-223. Bone supportive agents and palliative radiation continue to play an important role in the overall management of mCRPC. Given the complexity, variety and importance of optimizing the use of these agents, a multidisciplinary team approach is highly recommended.

Introduction

Castration-resistant prostate cancer (CRPC) is defined by disease progression despite castrate levels of testosterone and may present as either a continuous rise in serum prostate-specific antigen (PSA) levels, the progression of pre-existing disease, and/or the appearance of new metastases.

Advanced prostate cancer has been known under a few names over the years, including hormone-resistant prostate cancer (HRPC) and androgen-insensitive prostate cancer (AIPC). Most recently, the terms castration-resistant prostate cancer or castration-recurrent prostate cancer were introduced with the realization that extra-testicular androgen production plays a significant role in the resistance of prostate cancer cells to medical or surgical castration therapy.¹

In their second publication, the Prostate Cancer Working Group defined CRPC as a continuum on the basis of whether metastases are detectable (clinically or by imaging) and whether the serum testosterone is in the castrate range by surgical orchidectomy or medical therapy.² This definition creates a clinical-states model where patients can be classified. The rising PSA states (castrate and non-castrate) indi-

cates that no detectable (measurable or non-measurable) disease has ever been found. The clinical metastases states (castrate and non-castrate) signify that disease was detectable at some point in the past, regardless of whether it is detectable now.³

Prognosis is associated with several factors that go beyond PSA levels. These include performance status, presence of visceral metastases, presence of bone pain, extent of disease on bone scan, and serum lactate dehydrogenase and alkaline phosphatase levels. Bone metastases will occur in 90% of men with CRPC and can produce significant morbidity, including pain, pathologic fractures, spinal cord compression and bone marrow failure. Paraneoplastic effects, including anemia, weight loss, fatigue, hypercoagulability and increased susceptibility to infection, are also common.

CRPC includes patients without metastases or symptoms with rising PSA levels despite androgen deprivation therapy (ADT) to patients with metastases and significant debilitation due to cancer symptoms. Clinical scenarios are outlined in Table 1.

Management of CRPC

First- and second-line hormonal agents

Because the androgen receptor remains active in most patients who have developed castration-resistant disease, it is recommended that ADT be continued for the remainder of a patient's life (Level 3, Grade C).

In patients who develop CRPC, secondary hormonal treatments may be attempted (Level 3, Grade C).

To this date, no study of secondary hormone treatment has shown survival benefits; most trials have been small and were not designed to evaluate overall survival and were

heavily confounded by future treatments used. In patients treated with luteinizing hormone-releasing hormone (LHRH) agonist/antagonist monotherapy or who have had an orchidectomy, the addition of total androgen blockade (TAB) with androgen receptor antagonists, such as bicalutamide, can offer modest PSA responses that are short-lived in 30% to 35% of patients.⁴

For patients who have undergone TAB, the antiandrogen (AA) should be discontinued to test for an AA withdrawal response (AAWD). Introducing or changing AA or using corticosteroids with or without ketoconazole has been noted to cause transient PSA reductions in about 30% of patients (Level 3, Grade C).

Non-metastatic CRPC

There is no standard of care and no approved regimen in M0 CRPC. AA therapy should be discontinued if patients are receiving these agents. Secondary hormonal treatments may be attempted (Level 3, Grade C).

Detection of metastases and imaging

For patients who progress on ADT without evidence of distant metastases, it is suggested to screen for bone metastases with bone scans and monitor for lymph node and visceral metastases/progression with imaging of the abdomen/pelvis and chest.

Patients with a rapid PSA doubling time (PSADT (<8 months) are at risk for developing earlier metastases. Imaging in these patients should be performed every 3 to 6 months. Patients with a slower PSADT (>12 months) should be screened every 6 to 12 months (Expert Opinion). Imaging techniques most commonly used include nuclear bone scans and abdominal/pelvic computed tomography and chest X-ray. The role of magnetic resonance imaging (MRI) and positron-emission tomography is still unclear.

Treatment of metastatic CRPC (mCRPC)

Currently, only patients with CRPC who have detectable macroscopic metastatic disease should be considered for systemic therapy (i.e., new hormonal agents or chemotherapy) outside of a clinical trial. Patients with advanced prostate cancer should optimally receive multidisciplinary care to maximize survival and quality of life. Because any treatment for advanced disease remains non-curative, patients with advanced prostate cancer should be encouraged to participate in clinical trials.

1. Androgen receptor (AR) signaling therapeutic options

Novel agents that can affect the androgen receptor signaling have recently been developed and have renewed the enthusiasm for effective hormone manipulation. In men with

CRPC, phase III clinical trials have evaluated the role of abiraterone acetate and enzalutamide in both the chemo-naïve and post-chemotherapy settings.

Abiraterone acetate

Abiraterone acetate is a potent and irreversible inhibitor of CYP-17, a critical enzyme in androgen biosynthesis.

Chemo-naïve setting

Abiraterone acetate 1000 mg/day plus prednisone 5 mg twice daily is recommended for first-line therapy for asymptomatic or minimally symptomatic metastatic CRPC (Level 1, Grade A).

In asymptomatic or minimally symptomatic patients (defined as pain that is relieved by acetaminophen or a non-steroidal anti-inflammatory) without visceral metastases, abiraterone acetate significantly improved radiographic progression-free survival (PFS) (16.5 vs. 8.3 months) (hazard ratio [HR] 0.53; 95% confidence interval [CI] 0.45–0.62; $p < 0.001$). Abiraterone also significantly delayed time to pain progression, time to chemotherapy initiation, time to opiate initiation and deterioration of the Eastern Cooperative Oncology Group (ECOG) performance status. The final analysis of the study confirms a statistically significant 4.4 months improvement in overall survival (HR 0.81 $p = 0.0033$).⁵

Post-docetaxel setting

Abiraterone acetate (1000 mg per day) plus prednisone (5 mg twice daily) is recommended in patients progressing on or after docetaxel-based chemotherapy (Level 1, Grade A).

In the post-docetaxel setting, abiraterone-prednisone compared to placebo-prednisone has significantly prolonged median overall survival by 4.6 months (15.8 vs. 11.2 months; HR 0.74; $p = 0.0001$) in patients with mCRPC who had progressed after docetaxel treatment. Moreover, all secondary endpoints supported the superiority of abiraterone over placebo: median time to PSA progression (8.5 vs. 6.6 months; HR 0.63; $p < 0.0001$), radiographic PFS (5.6 vs. 3.6 months; HR 0.66; $p < 0.0001$), confirmed PSA response rate defined as $\geq 50\%$ reduction in PSA from the pre-treatment baseline PSA (29% vs. 5.5%; $p < 0.0001$) and objective response by Response Evaluation Criteria in Solid Tumors (RECIST) (14.8% vs. 3.3%; $p < 0.0001$).⁶

Enzalutamide

Enzalutamide is a potent multi-targeted androgen signalling pathway inhibitor.

Chemo-naïve setting

Enzalutamide (160 mg per day) is recommended as first-line therapy for asymptomatic or minimally symptomatic meta-

Table 1. Clinical scenarios and management options for patients with CRPC

CRPC includes a wide range of disease types: from patients without metastases or symptoms with rising PSA levels despite ADT to patients with metastases and significant debilitation due to cancer symptoms. **The panel recommends that ADT be continued in the presence of CRPC.**

1. Rising PSA non metastatic CRPC

There is no standard of care and no approved regimen in M0 CRPC. AA therapy should be discontinued if patients are receiving these agents. Secondary hormonal treatments (excluding abiraterone or enzalutamide) may be attempted (Level 3, Grade C).

Detection of metastases and imaging

It is suggested to screen for bone metastases with bone scans and monitor for lymph node and visceral metastases/progression with periodic imaging of the abdomen/pelvis and chest. Patients with a rapid PSADT (<8 months) are at risk for developing earlier metastases. Imaging in these patients should be performed every 3 to 6 months. Patients with slower PSADT (>12 months) should be screened every 6 to 12 months (Grade C).

2. Metastatic CRPC without symptoms or minimally symptomatic (defined as pain that is relieved by acetaminophen or a non-steroidal anti-inflammatory)

AA therapy should be discontinued if patients are on it to test for an AA withdrawal response.

Introduction of, or changes to, a first-generation AA or the use of corticosteroids with or without ketoconazole may be considered (Level 3, Grade C).

Abiraterone acetate 1000 mg/day plus prednisone 5 mg/twice daily is recommended as first-line therapy (Level 1, Grade A). Abiraterone acetate significantly improved overall survival, radiographic progression-free survival, time to pain progression and time to chemotherapy initiation; it also delayed ECOG performance status deterioration. The study did not include patients with visceral metastases.

Enzalutamide 160 mg/day is recommended as first-line therapy* (Level 1, Grade A). Enzalutamide significantly improved overall survival, progression free survival, time to pain progression, time to chemotherapy initiation and delayed ECOG performance status deterioration. The study included patients with visceral metastases.

Treatment with docetaxel 75 mg/m² every 3 weeks plus 5 mg oral prednisone twice daily can be offered (Level 1, Grade A). Docetaxel has been shown to improve overall survival, disease control, symptom palliation and quality of life. The timing of docetaxel therapy in men with evidence of metastases, but without symptoms, should be discussed with the patient and therapy should be individualized based on the patient's clinical status and preference.

3. Metastatic CRPC with symptoms

Treatment with docetaxel 75 mg/m² every 3 weeks plus 5 mg oral prednisone twice daily is recommended (Level 1, Grade A). Docetaxel has been shown to improve overall survival, disease control, symptom palliation and quality of life.

Radium-223 every 4 weeks for 6 cycles is recommended in patients with pain due to bone metastases and who do not have visceral metastases (Level 1, Grade A). Radium-223 significantly improved overall survival and reduced symptomatic skeletal related events in patients with symptomatic mCRPC who had previously received docetaxel chemotherapy or were deemed unfit for docetaxel.

Abiraterone acetate 1000 mg/day plus prednisone 5 mg twice daily or enzalutamide 160 mg/day may be considered as first-line therapy in patients who cannot receive or refused docetaxel (Expert opinion). The studies in chemotherapy-naïve patients did not include patients with moderate or severe pain; therefore, the efficacy is not well-documented in patients with significant symptoms.

4. Metastatic CRPC who progress after docetaxel-based chemotherapy**Options with survival benefit**

- Cabazitaxel (25 mg/m²) plus prednisone (5 mg/day) (Level 1, Grade A)
- Abiraterone acetate (1000 mg per day) plus prednisone (5 mg twice daily) (Level 1, Grade A)
- Enzalutamide (160 mg/day) (Level 1, Grade A)
- Radium-223 q 4 weeks for 6 cycles (Level 1 Grade A)

Options with unknown survival benefit

- Docetaxel plus prednisone re-exposure in patients who have had a previous favorable response to docetaxel may be reasonable (Expert Opinion). Mitoxantrone plus prednisone may be offered for palliative pain relief (Grade C).

5. Patients with CRPC and bone metastases (includes the pre or post chemotherapy settings)

In men with CRPC and bone metastases, denosumab (120 mg subcutaneous) or zoledronic acid (4 mg intravenous) every 4 weeks, along with daily calcium and vitamin D supplementation, is recommended to prevent disease-related skeletal complications (Level 1, Grade A).

*Pending Health Canada Approval in the chemo-naïve setting. CRPC: castration-resistant prostate cancer; ADT: androgen deprivation therapy; mCRPC: metastatic CRPC; PSA: prostate-specific antigen; AA: anti-androgen; PSADT: PSA doubling time; ECOG: Eastern Cooperative Oncology Group.

static CRPC (Level 1, Grade A). (Pending Health Canada approval in the chemo-naïve setting.)

In asymptomatic or minimally symptomatic patients (defined as pain that is relieved by acetaminophen or a non-steroidal anti-inflammatory), enzalutamide decreased the risk of radiographic progression or death by 81% (HR 0.19; 95% CI 0.15–0.23; $p < 0.001$) and the risk of death by 29% (HR 0.71; 95% CI 0.60–0.84; $p < 0.001$) as compared with placebo. The benefit of enzalutamide was demonstrated for all secondary endpoints, including time to initiation of cytotoxic chemotherapy time to first skeletal-related event (SRE), best overall soft tissue response (59% vs. 5%; $p < 0.001$), time to PSA progression (HR 0.17; $p < 0.001$), and $\geq 50\%$ PSA decline rate (78% vs. 4%; $p < 0.001$). Enzalutamide also significantly delayed time to pain progression, time to opiate initiation, and deterioration of the ECOG performance status.⁷

Post-docetaxel setting

Enzalutamide (160 mg per day) is recommended in patients progressing on or after docetaxel-based chemotherapy (Level 1, Grade A).

In patients previously treated with docetaxel the AFFIRM trial compared enzalutamide and placebo.^{8,9} The study demonstrated a significant advantage in overall survival of 4.8 months (18.4 vs. 13.6 months; HR 0.62; $p < 0.0001$) and all secondary endpoints, including confirmed PSA response rate (54% vs. 2%, $p < 0.001$), soft-tissue response rate (29% vs. 4%, $p < 0.001$), the time to PSA progression (8.3 vs. 3.0 months; HR 0.25; $p < 0.001$), radiographic PFS (8.3 vs. 2.9 months; HR 0.40; $p < 0.001$), and the time to the first SRE (16.7 vs. 13.3 months; HR 0.69; $p < 0.001$).

The studies in the chemo-naïve setting did not include patients with moderate or severe symptoms; however abiraterone and enzalutamide may be potential therapeutic options in patients who are deemed chemotherapy ineligible (Expert Opinion).

2. Chemotherapy

First-line systemic chemotherapy

Docetaxel 75 mg/m² intravenous (IV) every 3 weeks with 5 mg oral prednisone twice are recommended for patients with metastatic CRPC (Level 1, Grade A).

The TAX-327 study randomized 1006 patients to one of three treatment arms: (1) docetaxel (75 mg/m² IV, every 3 weeks); (2) docetaxel (30 mg/m², 5 times weekly for 5 of 6 weeks); or (3) control therapy with mitoxantrone.^{10,11} The study reported improved survival with docetaxel (every 3 weeks) compared with mitoxantrone-prednisone (median survival 18.9 vs. 16.5 months; HR 0.76 [95% CI 0.62–0.94], two-sided $p = 0.009$). No overall survival benefit was observed with docetaxel given on a weekly schedule (HR

0.91, [95% CI 0.75–1.11], two-sided $p = 0.36$). Significantly more patients treated with docetaxel (every 3 weeks) achieved a pain response compared with patients receiving mitoxantrone (35% vs. 22%, $p = 0.01$). Quality of life response, defined as a sustained 16-point or greater improvement from baseline on two consecutive measurements, was higher with docetaxel given every 3 weeks (22% vs. 13%, $p = 0.009$) or weekly (23% vs. 13%, $p = 0.005$) compared with mitoxantrone.

PSA response rates were also statistically significantly higher with docetaxel compared to mitoxantrone. In the 2 trials, 27% ($n = 412$) and 29% ($n = 196$) of patients had measurable disease.

Although patients received up to 10 cycles of treatment if no progression and no prohibitive toxicities were noted, the duration of therapy should be based on the assessment of benefit and toxicities. Rising PSA only should **not** be used as the sole criteria for progression; assessment of response should incorporate clinical and radiographic criteria.

Alternative therapies that have not demonstrated improvement in overall survival, but can provide disease control, palliation and improve quality of life, include weekly docetaxel plus prednisone, and mitoxantrone plus prednisone (Level 2, Grade B).¹²

The timing of docetaxel therapy in men with evidence of metastases, but without symptoms, should be discussed with patients and therapy should be individualized based on patients' clinical status and preferences (Level 3, Grade C).

Use of estramustine in combination with other cytotoxic agents is *not* recommended due to the increased risk of clinically important toxicities. There is no evidence to support the use of this combination to improve survival or palliation (Level 2, Grade C).

Neuroendocrine differentiation may be present in patients who do not respond to first-line ADT or who progress clinically or radiologically without significant PSA elevations. Biopsy of accessible lesions should be considered to identify these patients; these patients should then be treated with combination chemotherapy, such as cisplatin/etoposide or carboplatin/etoposide (Level 3, Grade C).

Second-line systemic chemotherapy

Cabazitaxel is recommended for mCRPC patients progressing on or following docetaxel (Level 1, Grade A).

A phase 3 study comparing cabazitaxel to mitoxantrone in patients previously treated with docetaxel has shown a statistically significant survival advantage.¹³ This randomized, placebo-controlled trial recruited 755 docetaxel pre-treated CRPC patients. Overall survival was the primary endpoint of the study. Patients were randomized to receive prednisone 10 mg/day with 3-weekly mitoxantrone 12 mg/m² or cabazitaxel 25 mg/m². An advantage in survival emerged

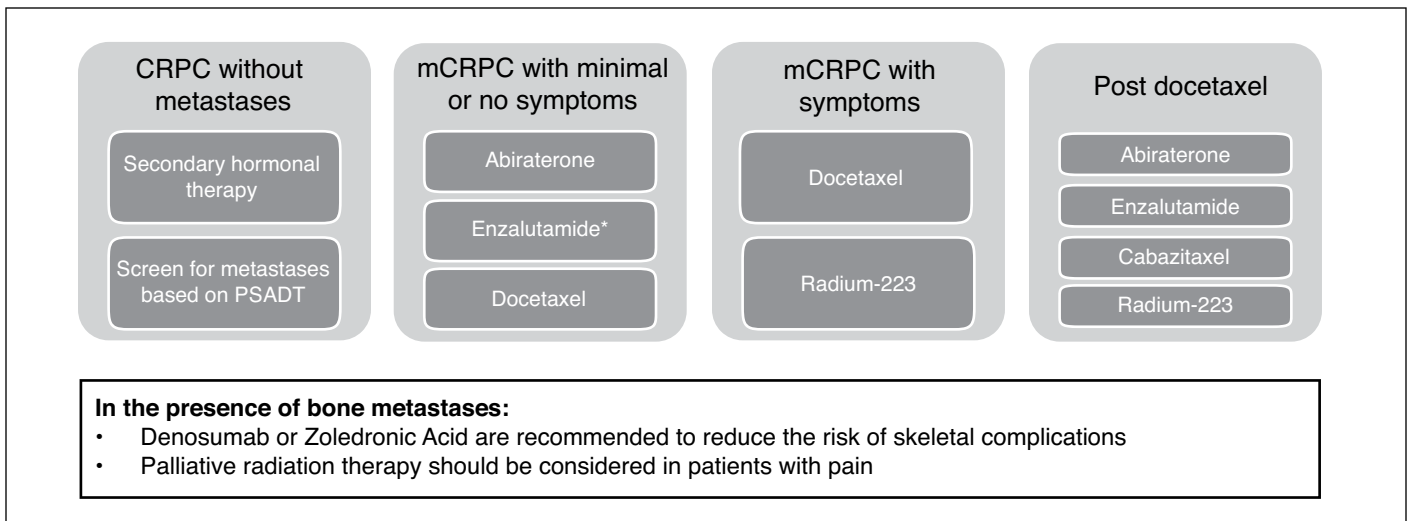


Fig. 1. Management of castration-resistant prostate cancer (CRPC). PSADT: prostate-specific antigen doubling time. mCRPC: metastatic CRPC. *Pending Health Canada approval in the chemo-naïve setting.

1. The optimal sequence of available options remains unknown.
2. Patients who have had little no response to hormonal agents OR who progress with minimal change in PSA or with significant visceral metastases should be considered for early chemotherapeutic options.
3. Radium-223 is not approved for patients with visceral metastases.
4. Whenever possible, clinical trials should remain the first choice in patients with CRPC.

in favour of the cabazitaxel group, with a median survival of 15.1 months compared with 12.7 months in the mitoxantrone group (HR 0.70; 95% CI 0.59–0.83; $p < 0.0001$).

Other options

For patients who have had a good response to first-line docetaxel re-treatment with docetaxel can be considered (Expert Opinion).¹⁴⁻¹⁶

Mitoxantrone may be considered a therapeutic option in symptomatic patients with mCRPC in the first- or second-line setting. Mitoxantrone has not shown any survival advantage, but may give symptomatic relief. Of note in the second-line setting, mitoxantrone has limited activity and increased toxicity (Grade C).

3. Bone-targeted therapy

Life-prolonging therapy

Radium-223

Radium-223 every 4 weeks for 6 cycles is recommended in patients with pain due to bone metastases and who do not have visceral metastases (Level 1, Grade A).

Radium-223 (previously known as alpharadin) is an intravenous alpha-emitting agent that mimics calcium preferentially targeting bone metastases. In a randomized phase III study, radium-223 given every 4 weeks for 6 cycles was compared to placebo.¹⁷ Radium-223 demonstrated a significant improvement in overall survival and symptomatic SRE. Overall survival was improved by 3.6 months

(HR 0.7, $p < 0.0001$) and SREs were delayed by 5.8 months ($p < 0.0001$). The study included patients with symptomatic bone metastases who were post-docetaxel or ineligible for docetaxel. The study excluded patients with visceral metastases. **Compared to PSA, alkaline phosphatase appears to be a better marker of activity given the mechanism of action of radium-223.**

Supportive agents

Denosumab and zoledronic acid

In men with CRPC and bone metastases, denosumab (120 mg subcutaneous [SC]) or zoledronic acid (4 mg IV) every 4 weeks are recommended to prevent disease-related SREs, including pathological fractures, spinal cord compression, surgery or radiation therapy to bone (Level 1, Grade A).

Bone loss associated with ADT has been shown to increase the risk of fracture.¹⁸⁻²² Moreover, about 90% of patients with mCRPC will develop bone metastases, which cause local decreases in bone integrity. Patients are at significant risk of SREs that include pathological fractures, debilitating bone pain requiring palliative radiation therapy and spinal cord compression. Quality of life is affected by these complications.

Zoledronic acid is a third-generation nitrogen containing bisphosphonate. Bisphosphonates other than zoledronic acid are not known to be effective to prevent disease-related SREs. In the placebo controlled zoledronic acid study, fewer men receiving zoledronic acid had SREs (38% vs. 49%,

$p = 0.02$).²³ Zoledronic acid also increased the median time to first SRE (488 vs. 321 days, $p = 0.01$). There was an overall 36% reduction in the rate of SREs in treated patients.

Treatment with zoledronic acid should not be used in men with baseline creatinine clearance <30 mL/min.

Denosumab is a fully humanized monoclonal antibody against RANK ligand. It has been shown to be effective in preventing bone loss and new vertebral fractures due to ADT.²² In the setting of mCRPC, denosumab (120 mg SC, every 4 weeks) compared to zoledronic acid (4 mg IV, every 4 weeks) has shown significant improvement in the time to the first SRE (20.7 vs. 17.1 months, $p < 0.001$ for non-inferiority; $p = 0.008$ for superiority), while overall survival and PFS were not different.²⁴

No dose modification for renal function is necessary in the case of denosumab; however, the risk of hypocalcaemia is increased and calcium monitoring and supplementation (with calcium and vitamin D) is recommended for both denosumab and zoledronic acid. Denosumab has not been studied in patients with severe renal impairment (glomerular filtration rate <30 mL/min).

Good oral hygiene, baseline dental evaluation for high-risk individuals, and avoidance of invasive dental surgery during therapy are recommended to reduce risk of osteonecrosis of the jaw (ONJ) for patients treated with bone-targeted therapies (Level 3, Grade C).²⁵⁻²⁷ Zoledronic acid and denosumab have been used in combination with all the agents presently in use for the treatment of mCRPC. To date there have been no additional safety issues of concern that have been reported.^{23,24}

The optimal duration of zoledronic acid and denosumab in men with CRPC and bone metastases is undefined. The risk of ONJ appears to be related to time on bone-targeted therapy; therefore caution should be taken in using these agents more than 2 years.²⁸

Denosumab and zoledronic acid are not approved and not indicated for bone metastases prevention in Canada.

4. Other supportive care therapies

Systemic corticosteroid therapy

Corticosteroid therapy with low-dose prednisone or dexamethasone may also offer improvements in PSA values and/or palliative outcomes in up to 30% of patients in both symptomatic and asymptomatic men. Steroids may also exert an anti-neoplastic effect on prostate cancer (Level 3, Grade C).^{29,30}

Palliative radiation

Bone metastases from prostate cancer are often radiosensitive and most men will experience partial or complete pain relief from external beam radiation to a specific lesion.

Studies have shown that a single fraction of standard palliative radiotherapy is as effective as 5 or more fractions in providing palliation. However, more patients require re-treatment for pain recurrence with single fraction radiation (Level 2, Grade B). Stereotactic body radiotherapy is a more precise and may be a more effective form of palliation delivered in 5 or fewer treatments and may also be considered (Level 3, Grade C).

Radionuclide therapy, in the form of systemic strontium-89 therapy, may be useful in the palliation of CRPC when multiple skeletal sites are involved in carefully selected patients. Risks include severe prolonged myelosuppression and transfusion dependence. Strontium-89 may be associated with a worse overall survival as compared to external beam radiotherapy.^{31,32}

Malignant spinal cord compression is an oncologic emergency that requires immediate diagnosis, if suspected, with an MRI. Options for treatment are debulking surgery + radiotherapy, vertebrectomy with stabilization and radiotherapy, or radiotherapy + steroids (Level 1, Grade A).³³

Conclusion

Advances in treatment for men with CRPC have improved survival and quality of life, but most, if not all, patients eventually succumb to their disease. Several new agents are being studied in all states of CRPC and an increase in options is likely in the near future.^{9,25-27,34-36} Because CRPC remains an incurable and ultimately fatal illness, inclusion of patients in clinical trials remains paramount.

Notes: MEDLINE search of the English language and conference proceedings were used to produce the present document. Wherever Level 1 evidence is lacking, the guideline attempts to provide expert opinion to aid in the management of patients. Levels of evidence and grades of recommendation employing the International Consultation on Urologic Disease (ICUD)/WHO modified Oxford Center for Evidence-Based Medicine grading system were applied.

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advisory boards for Amgen, Janssen, and Astellas. He also holds the patent on a product for CDRD. He is currently participating in a clinical trial with Amgen, Cougar, Janssen, Astellas. Dr. Usmani is a member of the advisory boards for Astellas, Johnson & Johnson, and Amgen. He has also received grants from Best Medical and Varian Medical Systems. Dr. Fleshner is a member of the advisory boards for Amgen, Janssen, Astellas and Eli Lilly. He has received honoraria from Amgen, Janssen, Astellas, and Eli Lilly. He is and has participated in clinical trials for Amgen, Janssen, Medivation, OICR, and Prostate Cancer Canada. Dr. Hotte, Dr. North, and Dr. Vignault declare no competing financial or personal interests.

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